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Safety and Mid-to-Long-term Outcome

of

Carotid Artery Stenting

Inaugural-Dissertation
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vorgelegt von
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1. Abstract

Background:

The value of carotid artery stenting (CAS) for the treatment of symptomatic and asymptomatic carotid artery stenosis is still questioned despite its tremendous increase in recent years. We analysed the safety and outcome of carotid artery stenting in a prospective CAS registry at a tertiary teaching hospital.

Methods:

Between July 2003 and January 2009, baseline characteristics, procedural and follow-up data including duplex sonography of the carotid artery were prospectively collected from all patients undergoing CAS. Primary endpoint was defined as 30-day major adverse events (MAE), including death, any stroke or myocardial infarction, and mid- to long-term follow-up outcome included ipsilateral stroke, myocardial infarction or death. Secondary endpoint was defined as restenosis ≥ 50 %.

Results:

173 patients underwent 187 CAS procedures, of which one third was performed for a symptomatic carotid artery stenosis. In 13 patients CAS was performed bilaterally as staged procedures. The 30-day MAE rate was 1.6 % consisting of two contralateral strokes and one ipsilateral stroke. Mean follow-up time was 29.3 months. Mid- to long-term MAE was 9.8% with 6.9% (n=12) deaths, 2.3% (n=4) myocardial infarctions and 0.6% (n=1) ipsilateral stroke. The restenosis rate was 5.3 % after a mean follow-up of 22 months (range 2-73) of which only one required a reintervention because of restenosis of > 70% at 9 months follow-up.

Conclusion:

Carotid artery stenting at a tertiary, teaching hospital is safe and shows an excellent patency rate. The low adverse event rate indicates an appropriate patient selection.

2. Introduction

Stroke is one of the leading causes of death following ischemic heart disease and is one of the most frequent reasons of permanent disability [1]. It has been estimated that significant stenosis of the internal carotid artery may be the predisposing condition in 5-12 % of all strokes [2]. Carotid endarterectomy has been shown to reduce the risk of recurrent stroke by 50% in patients with recent cerebrovascular symptoms associated with severe carotid artery stenosis [3]. Endovascular treatment with balloon angioplasty and stent implantation is an accepted alternative to endarterectomy [4]. However, a meta-analysis found a higher risk for stroke or death within 30 days after endovascular intervention [5]. Therefore, endarterectomy has remained the treatment of choice for carotid artery stenosis [5]. Recent results from the CAVATAS study have shown that the restenosis rate is higher after endovascular treatment than after endarterectomy, however in this study 75 % of patients have only be treated with balloon angioplasty without stent implantation [6].

In contrast, the “Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy” (SAPPHIRE) trial suggested that CAS may have a better outcome than CEA in selected, high risk patients [7]. In contrast, the SPACE trial (Stent Protected Angioplasty versus Carotid Endarterectomy) failed to prove the non-inferiority of CAS for the 30-day complication rate but showed similar results at two years follow-up [8].

In summary, despite all results from randomized trials the optimal indication for CAS remains unclear. While the EVA-3S trial has been criticized for the limited interventional experience requested for participation in the study [9], consensus on minimal training requirements and performance data of newly initiated CAS programs are lacking.

Recently we reported on the safety of starting an interdisciplinary CAS program in 100 patients [10]. In the present analysis, we report the continuation of that program, with special focus on 30-day event rate and mid-term patency rate in a teaching hospital.

3. Patients and Methods

3.1. Carotid stenting program and patient selection

Within a 2003 initiated academic CAS program, baseline patient characteristics, procedural data, and outcomes were prospectively entered in a database. The outcomes of the first 100 consecutive patients, treated between July 2003 and November 2006, were reported [10]. Further 73 patients were treated by CAS between November 2006 and January 2009. Interventionalists experience following a CAS-fellowship-training was reported in detail previously. In brief, in addition to full training in coronary or peripheral interventions, prior experience includes 100 diagnostic cerebral angiographies and 40 CAS procedures performed as first or second operator under supervision of an experienced interventionalist.
Patients were considered for revascularization in the presence of a ≥ 70 % asymptomatic or a ≥ 50 % symptomatic stenosis of the internal carotid artery.

Figure 1: Selective digital subtraction angiography of the left carotid bifurcation with a severe stenosis in a 69 year old female patient.

Stenosis was considered symptomatic in the presence of transient ischemic attack or stroke affecting the corresponding territory in the preceding six months. Stenosis severity was assessed by colour-coded duplexsonography (CCDS) and either confirmed by CT-, MR- or conventional angiography. In all patients a baseline imaging of the brain with CT or MR was performed and analysed by an independant neurologist. The indication for revascularization was made by the neurologist in all cases. After complete workup including neurological examination the indication for CAS was made by the neurologist. All patients underwent neurological examination the day after the intervention by the same neurologist. ECG and creatinin kinase (CK), CK-MB, and troponin were obtained on admission and one day after the procedure.

3.2. Technique

All patients were pretreated with aspirin 100mg and clopidogrel 75mg. During the procedure unfractionated heparin was administered to achieve an activated clotting time of 250-300 sec. Four-vessel angiography, consisting of at least a selective angiography of both common carotid arteries and a nonselective angiography of the subclavian and vertebral arteries was performed using a 5F diagnostic catheter. Extracranial and intracranial digital subtraction angiography of each vessel was obtained. The stenting procedure was performed wih either a 8F guiding catheter advanced over a 125 cm-long 5F diagnostic catheter with telescoping technique or a 6F 90cm-long sheath.

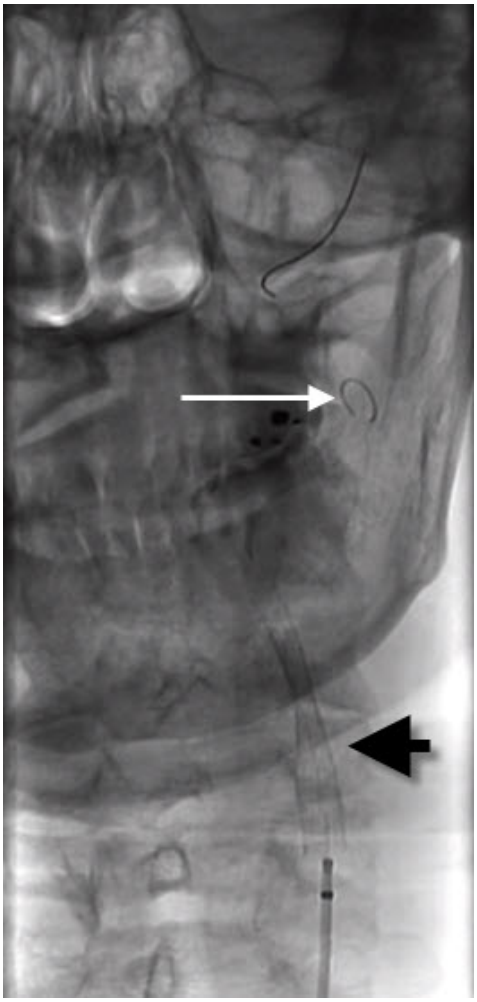

Figure 2: Antero-posterior fluoroscopic view with protection filter (white arrow) in place distally to the implanted stent (black arrow).

All procedures were performed with proximal or distal embolic protection devices (EPD) according to the discretion of the interventionalist and vascular conditions. To prevent bradycardia and hypotension, 0.5-1.0 mg of atropine was routinely administered intravenously prior to balloon inflation or prior to stenting if no predilatation was performed. After placement of the protection device predilation was usually performed with a 3.5mm to 4.5 mm balloon catheter (Invatec) before stent deployment, followed by postdilation (5.0mm-6.5mm). Choice of stent was at the discretion of the interventionalist (taped, open versus closed cell design). Before retrieval of the protection device, final biplane angiograms of the stented lesion as well as intracranial views were obtained.

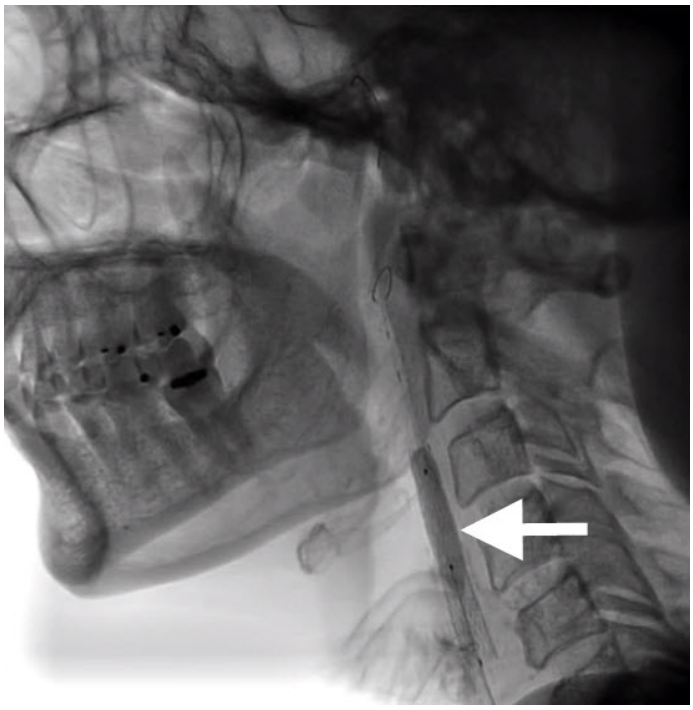

Figure 3: Lateral fluoroscopic view of balloon dilatation of the implanted stented in the left carotid bifurcation

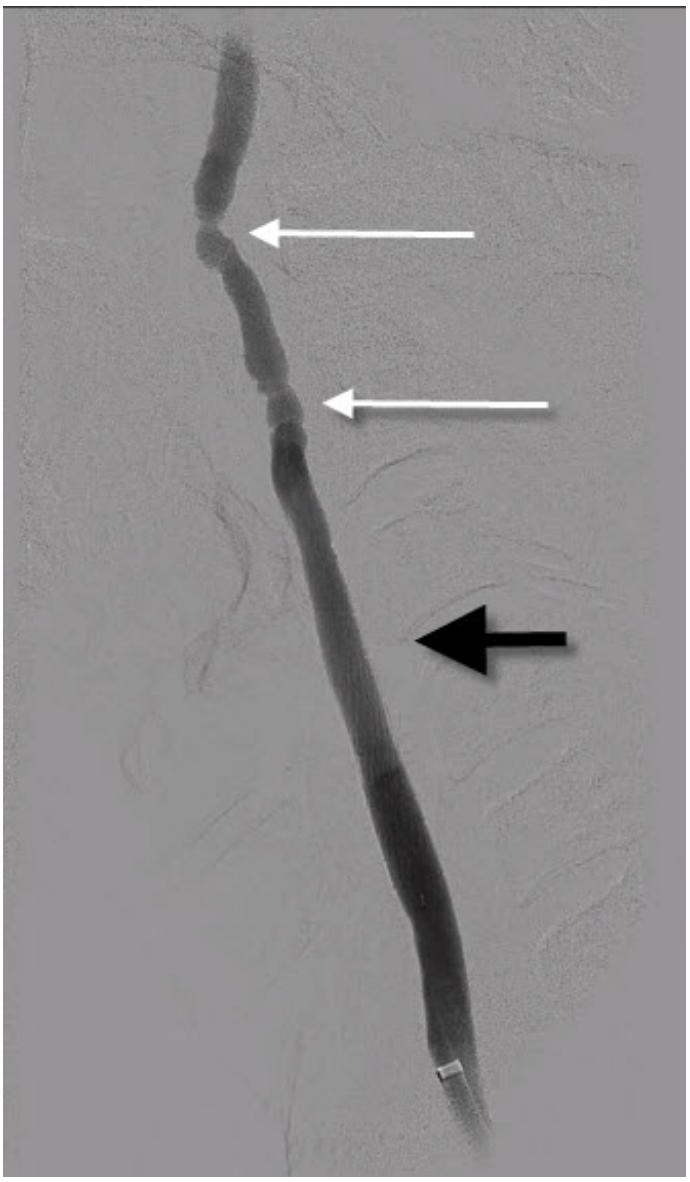

Figure 4: Lateral view and digital subtraction angiography following stent implantation (black arrow) and balloon dilatation. There is no residual stenosis in the area of stent implantation but mild non-flow limiting spasm of the distal part of the internal carotid artery (white arrows).

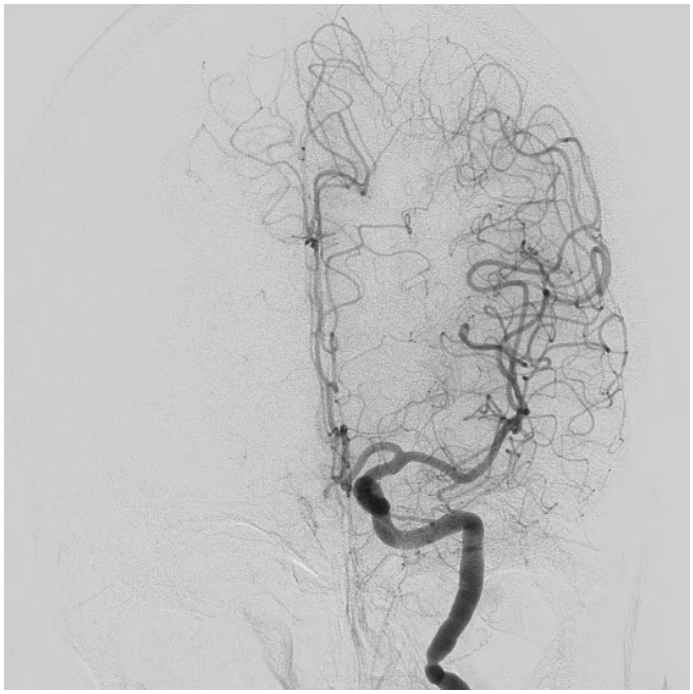

Figure 5: Antero-posterior view and digital subtraction angiography of the left intracranial blood flow without evidence for distal embolization following carotid artery stent implantation.

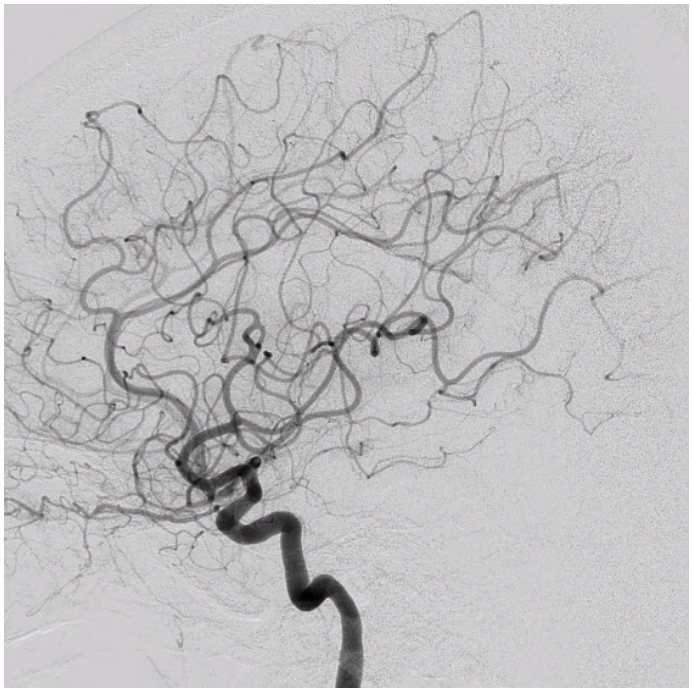

Figure 6: Lateral view of cerebral digital subtraction angiogram following selective left internal carotid artery injection following carotid artery stenting.

3.3. Outcome measures

Follow-up consisted of CCDS and clinical examination at 1 month, 6 months and 12 months, and yearly thereafter. The primary outcome measures were in accordance to the SAPPHIRE trial. [7] At 30 days, major adverse events (MAE) consisted of the composite occurrence of death, stroke, or myocardial infarction (MI). In addition, death, any stroke or myocardial infarction at follow-up was tracked. Minor stroke was defined as focal neurological deficit lasting more than 24 hours with ranking score ≤ 2 and NIH stroke score ≤4, while major stroke was diagnosed in the presence of a ranking score > 3 or NIH score ≥ 15. Any rise in CK-MB or troponin or new pathological Q-waves on ECG defined MI. Restenosis was diagnosed in the presence of a ≥ 50 % luminal narrowing as assessed by flow velocities using CCDS [10]. The peak systolic velocities and the end diastolic velocities of the common and the internal carotid arteries were recorded with CCDS. Technical success was defined by the coverage of the carotid lesion with a stent in the presence of a residual stenosis of less than 50 %. Stenosis was classified as: not significant (0–49% stenosis), moderate (50–69%), severe (70–99%).

3.4. Statistics

Continuous variables were expressed as mean ± standard deviation. Categorical data were presented as actual numbers and percentages.

4. Results

Between July 2003 and January 2009, 183 patients had an angiography with intention for CAS. Ten patients were excluded from the analysis for the following reasons: In seven patients undergoing diagnostic angiography the revascularization procedure was not performed because of absence of severe stenosis (n = 5) or occlusion of the carotid artery (n = 2), respectively. In addition, three patients were referred to carotid endarterectomy because of severe vessel tortuosity and hence high risk for CAS. In the above mentioned ten patients the procedure was stopped without any neurological or cardiovascular complications. Unilateral carotid artery interventions were performed in in 160 patients. One reintervention was performed in one patient because of restenosis at 9 months. Thirteen patients underwent bilateral staged CAS resulting in a total of 173 patients and 187 interventions. Of these 173 patients undergoing 187 procedures, analysis were performed per procedures for the 30-day major adverse event rate and per patients for the mid- to long term follow-up.

Mean age was 68 years (range 38-87). Comorbidities were previous cardiac intervention in 47% of the patients and in 88% other cardiovascular problems were present (i.e. congestive heart failure, previous myocardial infarction or previous cerebrovascular events). This is a relatively high prevalence of cardiovascular comorbidities compared to the SAPPHIRE trial with one or more high risk features in 54 % of the cases. One third of our patients presented with symptomatic carotid artery stenosis, 11 % had a contralateral carotid artery occlusion and 6% had a restenosis after CEA (Table I).

Technical procedural success was achieved in all cases (Table II). EPD`s were used in 98% of the procedures, of which a proximal EPD was used in 13 patients. Only in 2% no EPD was used due to severe tortuosity of the internal carotid artery. The lesions were predilated in 76 % and postdilated in 96 % of all procedures. One stent per procedure was used in 96 %. In six

patients more than one stent was necessary to cover the lesion. In one patient, an additional stent was necessary to cover a dissection caused by the guiding catheter.

During the CAS procedure in 18 (10%) patients an internal carotid artery spasm occurred which resolved either spontaneously or after administration of intraarterial nitroglycerine without any neurological complications. One patient had a seizure due to a longer period of hypotension during the intervention that spontaneously resolved. Periinterventional hemoglobin drop was observed in five patients without any postinterventional relevant bleeding at the access site, and most probably explained by the large volume of intravenously given fluid and the blood loss through the catheters during the procedure. Six patients with access groin hematomas were treated conservatively and no other access site complications were observed.

4.1. 30-day outcome

Major adverse event (MAE) rate within 30 days was 1.6 %. Three patients suffered a stroke, two of them were contralateral. The major ipsilateral stroke was the result of an air embolisation during balloon dilatation caused by a balloon defect [10]. The other two contralateral strokes (one minor, one major) were most likely due to periinterventional embolisation because of guiding catheter manipulation in the aortic arch. There were no deaths or MI within 30 days. There were 4% (2/50) major adverse events in symptomatic and 0.7% (1/137) in asymptomatic carotid artery stenosis..

4.3. Mid-and long-term follow-up

The mean follow-up was 29.3 months with a follow-up range from 2-72 months. During follow-up, 12 patients had died (6.9%), four suffered a stroke (2.3%) and four had a MI (2.3%). The causes of death were the following: four patients with refractory heart failure, three with cancer (prostate, stomach, bottom lip), one committed suicide, one suffered a

rupture of an aortic aneurysm, one died as a consequence of chronic heart- and kidney insufficiency, atrial fibrillation, and chronic obstructive pulmonary disease, and in two patients the cause of death was not identified (one had an intracranial bleeding six months before death and suffered from coronary heart disease with chronic atrial fibrillation occurring six months after CAS, the other with diabetes mellitus type II, mild insufficiency of the mitral and aortic valve and diastolic dysfunction with an ejection fraction of 62 % died 23 months after CAS).

The four minor strokes were the same as published in the previous report [10]. One was the result of a thrombotic stent occlusion 17 months after CAS in a patient who had been treated with four endarterectomies because of recurrent restenosis previously. One contralateral minor stroke had occurred during surgical replacement of the aortic valve two months after CAS. The third stroke was due to an occlusion of the contralateral retinal artery by a thrombus nine months after CAS in the presence of contralateral internal carotid artery occlusion. The fourth contralateral stroke occurred 30 months after CAS and the patient died 37 months after CAS.

A total of four MIs were registered during follow-up. Two MIs occurred in two patients with a known coronary artery disease, 20 respectively 40 months after CAS. One suffered a MI during aorto-coranary bypass surgery six weeks after CAS and the fourth MI was observed 40 months post CAS in a patient with newly detected coronary heart disease manifested with an acute biventricular cardial decompensation with dyspnea NYHA grade II and progredient angina pectoris.

The overall MAE at follow-up was 9.2 % (Table IV). The overall death or any stroke rate was 11 %. CCDS was performed in 74 % of all cases (139/187) six months after CAS. The restenosis rate was 5.3 % (8 patients and 9 vessels with a restenosis $\geq$ 50%, respectively, and one patient with a stent occlusion). Target lesion revascularization was performed in one patient only due to an asymptomatic restenosis detected 9 months after CAS.

Table I. Baseline Characteristics

	n = 173
Mean age, years	68
Range age ,years	38 - 87
Age > 80 years, n (%)	15 (9)
male gender, n (%)	126 (73)
Cardiovascular risk factors, n (%)	
Diabetes mellitus	43 (25)
Dislipidämia	139 (80)
Hypertension	150 (87)
Current smoking	56 (32)
History of cardiovascular disease, n (%)	
Previous PCI	93 (54)
Previous CAGB	81 (47)
Previous myocardial infarction	43 (25)
Congestive heart failure	13 (8)
Previous CEA ipsilateral	12 (7)
Previous CEA contralateral	9 (5)
Previous cerebrovascular event	95 (55)
SAPPHIRE high risk characteristics, n (%)	
≥ 1 high risk feature	77 (45)
≥2 high risk features	15 (9)
Carotid lesion characteristics, n (%)	n = 187
Symptomatic stenosis *	50 (27)
Contralateral occlusion	20 (11)
Contralateral stenosis ≥ 50%	63 (34)
Restenosis after endarterectomy	12 (6)

PCI; percutaneous coronary intervention; CABG; coronary artery bypass grafting

CEA; carotid endarterectomy; TIA, transient ischemic attack

SAPPHIRE; Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial

*TIA or CVI (cerebrovascular insult) in the preceding 6 months

Table II. Procedural Data

	n = 187
Angiographic and Doppler parameters	
Mean angiographic degree of stenosis,% [1]	83
Doppler flow velocities [2]	
Vmax (cm/sec) ICA systolic/diastolic (SD)	342/121 (117/58)
Vmax ICA/Vmax CCA (SD)	6 (2.71)
Drug regimen, n (%)	
Pretreatment with aspirin and clopidogrel [3]	186 (99)
Atropin administration	158 (85)
Any periprocedural norepinephrine	56 (30)
Norepidephrine boluses	55 (29)
Norepidephrine drip at end of procedure	16 (9)
Unfractionated heparin	187 (100)
Technical characteristics, n (%)	
Procedural success	187 (100)
Emboli protection device use	183 (98)
Angioguard	76 (41)
Spider	15 (8)
Filterwire	53 (28)
Emboshield	26 (14)
Ballon occlusion device	13 (7)
Stents, n (%)	187 (100)
More than 1 stent	6 (3)
Type of stent	
Precise	129 (69)
Acculink, Braun, Herculink, Bigsize	6 (3)
Vivexx	15 (8)
Nexstent	4 (2)
Cristallo	25 (13)
Vascuflex	8 (4)
Postdilatation, n (%)	180 (96)

[1] visual estimated

[2] Vmax; maximum velocity; ICA; internal carotid artery; CCA; common carotid artery

[3] One patient with aspirin allergy was treated periprocedurally with additional tirofiban and discharged on clopidogrel 150 mg/day for 1 month and 75 mg/day indefinitely. SD: standard deviation

Table III. Periprocedural Findings and Complications of the 187 procedures

	n (%)
Internal carotid artery spasm	18 (10)
Seizure	1 (1)
Blood Transfusion	6 (3)
Femoral pseudoaneurysm, arteriovenous fistulas, dessection	0
Endovascular or surgical treatment of femoral access required	0

Table IV. Major Adverse Events

	n (%)
Within 30 days	187 procedures
Death	0
Stroke	3 (1.6)
Major ipsilateral	1 (0.5)
Major nonipsilateral	1 (0.5)
Minor ipsilateral	0
Minor nonipsilateral	1 (0.5)
Myocardial infarction	0
Death, Stroke or Myocardial infarction	3 (1.6)
After 30 days	173 patients
Death	12 (6.9)
Stroke	4 (2.3)
Major ipsilateral	0
Major nonipsilateral	0
Minor ipsilateral	1 (0.6)
Minor nonipsilateral	3 (1.7)
Myocardial infarction	4 (2.3)
Overall	173 patients
Death, Stroke or Myocardial infarction at 30 days plus death or ipsilateral stroke within 31 days of follow-up	16 (9.2)
Death or any Stroke	19 (11)

Major adverse event rates were analyzed per procedure for the 30 days post procedure and per patients for the mid-to-long-term follow up

5. Discussion

The analysis of 173 patients treated with CAS at a tertiary referral hospital within a specific carotid stenting program demonstrates the short-and long-term safety regarding relevant end points well according to current recommendation guidelines.

All carotid stenosis, exept three lesions, could be successfully treated. In 98 % of the procedures emboli protection devices (EPD) has been used without any complications. The benefit of EPDs has not been established in randomized controlled trials, and available data are conflicting [11]. In our trial the 30 days-stroke-rate by using EPDs is 1.6 %, well aware of the causes of the three periinterventional strokes: one due to an air embolisation and two caused by guidining catheter embolisation in the aortic arch before EPD was implanted.

The MAE rate within 30 days was 1.6 %, corresponding to three periinterventional strokes and is lower than the internationally guidelines that require event rates of <3 % and < 6% for asymptomatic and symptomatic patients [12]. The overall ipsilateral stroke rate of only 1.2 % and the restenosis rate of 5.3 % at follow-up demonstrate the safety of the procedure and the mid- to long-term durability. Reported rates of early restenosis after CAS vary widely. Newly published long-term results concerning restenosis rate in the CAVATS study showed a three time higher incidence of developping a restenosis of ≥ 50 % in endovascular than after endarterectomy [6]. In this trial the incidence of restenosis rate after endovascular treatment by balloon dilatation was significally higher than with a stent. From the 50 patients who recieved a stent, 23 % of them after one year and 37 % after five years, respectively, developped a restenosis of ≥ 50 %, which is definitively higher than in our trial. This trial also demonstrated, that the greatest part of the restenoses occured after one year follow-up in each

surgical group, means that our restenosis rate result by a mean ultrasound follow-up of 22 months is well representativ.

No periprocedural myocardial infarction was observed, even though cardiac heart enzyms and ECG were routinely controled. That confirms the fact firstly described in SAPPHIRE trial, namely that the one-year-MAE- rate, means death, stroke and newly also MI included, was significantly lower in CAS than in CEA group, largely due to the higher incidence of perioperative MI in the CEA group [7]. That`s an important point because it`s known that patients with a carotid stenosis have a higher prevalence of coronary artery disease despite the abscence of cardiac symptoms [14].

The overall MAE-rate (9.2 %) according to SAPPHIRE and the Death-or-any-Stroke-rate (11 %) are mostly driven by the higher incidence of death in comparisation with the other MAE-factors but not correlating with long-term side effects or complications of CAS. The incidence of death is not surprising considered the mean age of 68 years and the high incidence of comorbidities.

In conclusion our trial suggests that CAS is a safe method for treatment with good short-and-long-term results.

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8. Curriculum vitae

Personal data

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Education

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